Review Article

# Pharmacovigilance in radiopharmaceuticals

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ABSTRACT

Indian Pharmacopoeia Commission is Committed for maintaining the standards of drugs including Radiopharmaceuticals (RPs) by publishing Indian Pharmacopoeia. These RPs are being used in India for diagnostic or therapeutic purpose. RPs though contain relatively small quantities of active ingredient and administered in small volumes could cause some adverse reactions to the patients. The objective of presenting this article is to introduce the system of adverse drug reaction reporting to the nuclear medicine fraternity who are dealing with RPs.

**Keywords:** Adverse drug reactions, pharmacovigilance, radiopharmaceuticals

## INTRODUCTION

Radiopharmaceuticals (RPs) are unique medicinal formulations containing radioisotopes, which are used in a variety of clinical conditions for diagnosis and/or therapy. The facilities and procedures for the production, use, and storage of RPs are subject to licensing by national and/or regional authorities. This licensing includes compliance with regulations governing RP preparations and those governing radioactive materials. Additional regulations may apply for issues such as transportation or dispensing of RPs.[1]

Pharmacovigilance (PV) process is defined as the science and activity relating to the detection, assessment, understanding, and prevention of adverse effects, or any other drug-related problem came into existence to monitor the Adverse Drug Reactions (ADRs) throughout the life period of a drug.[2] In India, the Ministry of Health and Family Welfare (MoHFW), Government of India, launched a nationwide Pharmacovigilance Programme of India (PvPI) in the year 2010 to monitor the safety of all drugs including topical medicines. Indian Pharmacopoeia Commission (IPC) under the MoHFW functions as National Coordination Centre (NCC) for PvPI. NCC identified 179 ADRs monitoring centres (AMCs) across the country to monitor, identify, and report ADRs to NCC.[3,4] ADR is response to a drug which is noxious and unintended and which occurs at doses normally used in human for the prophylaxis, diagnosis or treatment of a disease, or for the modification of physiological function can be reported to AMC-PvPI. A dedicated and trained team at AMC collects, manages, and assesses the report before submitting to NCC. ADRs reporter (healthcare professionals) who is not a part of AMC can report ADRs with all medicines including RPs whether known or unknown, serious or nonserious, and frequent or rare by filling the suspected ADR reporting form and submitting it to a nearby AMC [Figures 1 and 2] (also available in www.ipc.gov.in). A dedicated helpline (1800 180 3024) system is also available to provide assistance in ADRs reporting.[3] The obtained information is entered in the drug safety database, analyzed and assessed by the experts to identify new signals. This is also used as the main source for identifying and reducing the risks associated with the drugs used as RPs and others.[5-7]

The IPC has initiated efforts to include RPs, used in the field of nuclear medicine, as tracers in the diagnosis and treatment of various diseases including cancer, in the Indian Pharmacopoeia (IP) for the 2nd time in the Addendum-2015

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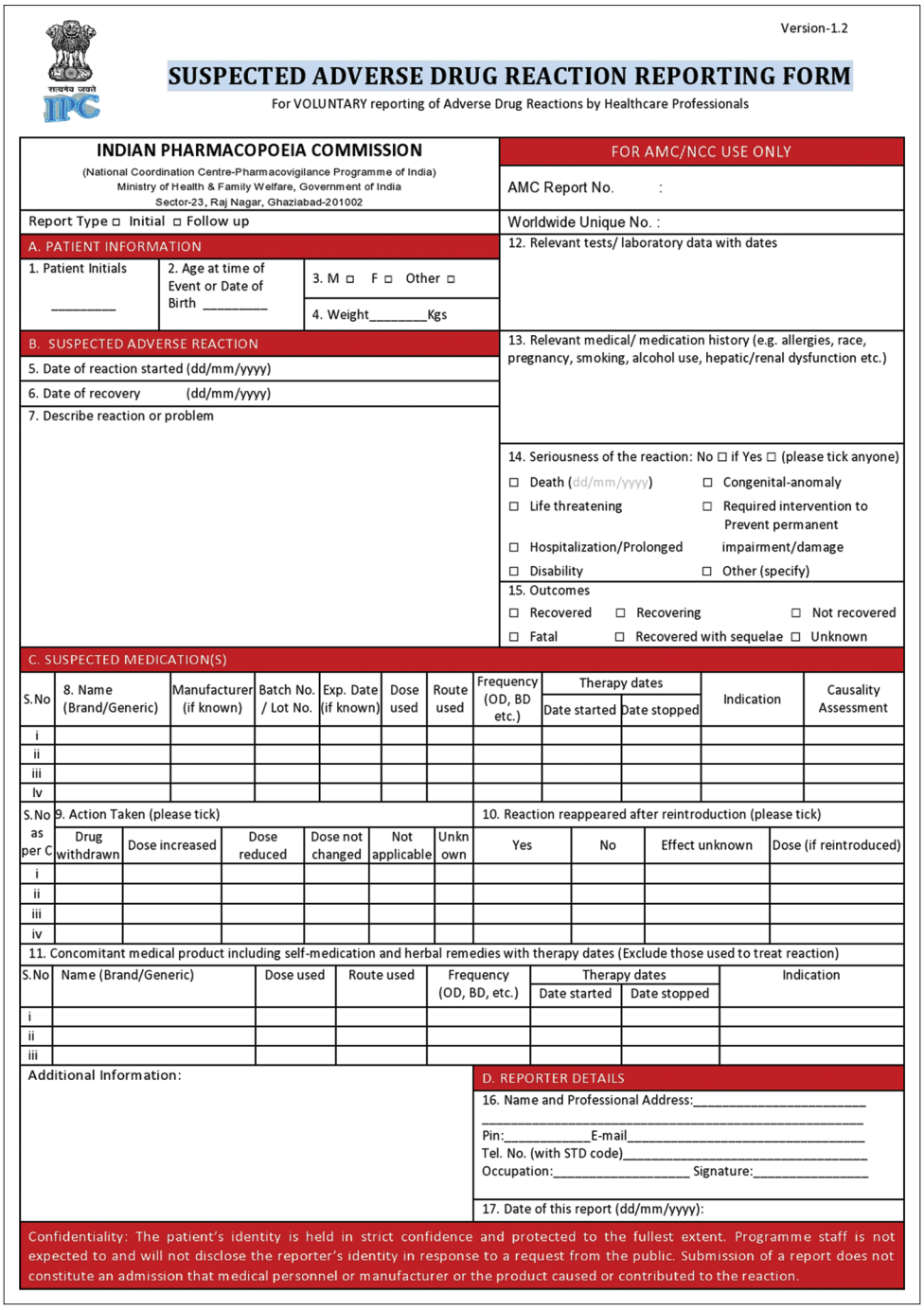


Version-1.2

सत्यमेव जयते
IPC

**SUSPECTED ADVERSE DRUG REACTION REPORTING FORM**

For VOLUNTARY reporting of Adverse Drug Reactions by Healthcare Professionals

**INDIAN PHARMACOPOEIA COMMISSION**
(National Coordination Centre-Pharmacovigilance Programme of India)
Ministry of Health & Family Welfare, Government of India
Sector-23, Raj Nagar, Ghaziabad-201002

FOR AMC/NCC USE ONLY

AMC Report No. :

Report Type ☐ Initial ☐ Follow up

Worldwide Unique No. :

A. PATIENT INFORMATION

1. Patient Initials _____

2. Age at time of Event or Date of Birth _____

3. M ☐ F ☐ Other ☐

4. Weight_____Kgs

12. Relevant tests/ laboratory data with dates

B. SUSPECTED ADVERSE REACTION

5. Date of reaction started (dd/mm/yyyy)

6. Date of recovery (dd/mm/yyyy)

7. Describe reaction or problem

13. Relevant medical/ medication history (e.g. allergies, race, pregnancy, smoking, alcohol use, hepatic/renal dysfunction etc.)

14. Seriousness of the reaction: No ☐ if Yes ☐ (please tick anyone)

☐ Death (dd/mm/yyyy) ☐ Congenital-anomaly
☐ Life threatening ☐ Required intervention to Prevent permanent
☐ Hospitalization/Prolonged impairment/damage
☐ Disability ☐ Other (specify)

15. Outcomes

☐ Recovered ☐ Recovering ☐ Not recovered
☐ Fatal ☐ Recovered with sequelae ☐ Unknown

C. SUSPECTED MEDICATION(S)

| S.No | 8. Name (Brand/Generic) | Manufacturer (if known) | Batch No. / Lot No. | Exp. Date (if known) | Dose used | Route used | Frequency (OD, BD etc.) | Therapy dates | | Indication | Causality Assessment |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Date started | Date stopped | | |
| i | | | | | | | | | | | |
| ii | | | | | | | | | | | |
| iii | | | | | | | | | | | |
| Iv | | | | | | | | | | | |

| S.No as per C | 9. Action Taken (please tick) | | | | | | 10. Reaction reappeared after reintroduction (please tick) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Drug withdrawn | Dose increased | Dose reduced | Dose not changed | Not applicable | Unknown | Yes | No | Effect unknown | Dose (if reintroduced) |
| i | | | | | | | | | | |
| ii | | | | | | | | | | |
| iii | | | | | | | | | | |
| iv | | | | | | | | | | |

11. Concomitant medical product including self-medication and herbal remedies with therapy dates (Exclude those used to treat reaction)

| S.No | Name (Brand/Generic) | Dose used | Route used | Frequency (OD, BD, etc.) | Therapy dates | | Indication |
|---|---|---|---|---|---|---|---|
| | | | | | Date started | Date stopped | |
| i | | | | | | | |
| ii | | | | | | | |
| iii | | | | | | | |

Additional Information:

D. REPORTER DETAILS

16. Name and Professional Address:_____
_____
Pin:_____E-mail_____
Tel. No. (with STD code)_____
Occupation:_____ Signature:_____

17. Date of this report (dd/mm/yyyy):

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

**Figure 1:** Front side of suspected adverse drug reaction reporting form

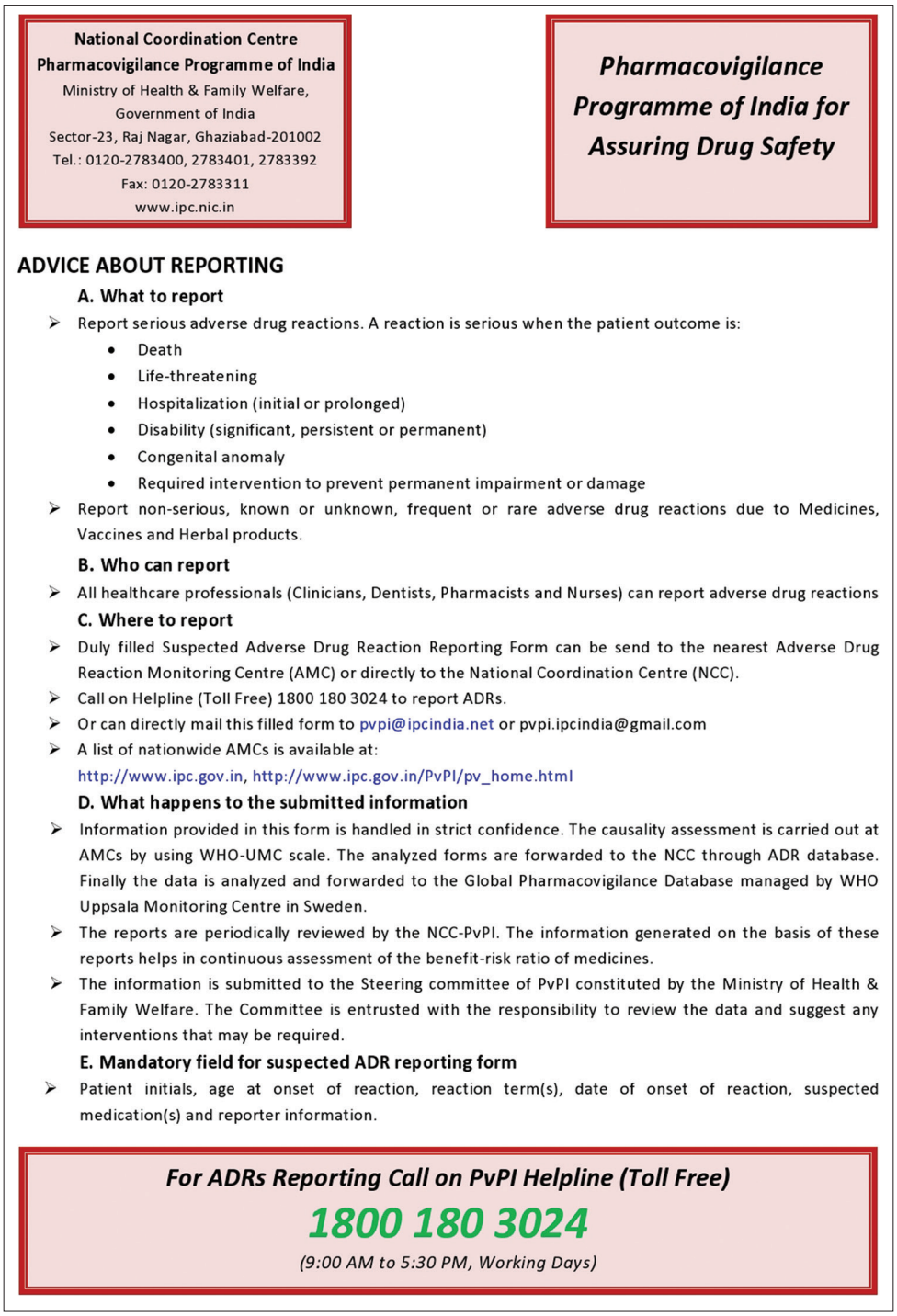
to IP in the year 2014 (IP-2014) and continuously working on other nuclear substances to include in the IP's next Addendum-2016.

The effort of IPC is to keep pace with emerging and contemporary areas for addressing the issues of healthcare requirements, in tandem with the regulatory developments in the global pharma sector.

The RPs are already included in advanced pharmacopoeias in developed countries. The World Health Organization has also provided more importance to the radioisotopes in its International Pharmacopoeia, of late. The IPC's efforts to address the segment are to keep the IP on par with these standards.

There were 19 monographs of RPs published in IP-2014. These are as follows:

Fluorodeoxyglucose ($^{18}$F) injection, ($^{131}$I) meta-iodobenzyl guanidine injection for diagnostic use, ($^{131}$I) meta-Iodobenzyl guanidine injection for therapeutic use, samarium ($^{153}$Sm) ethylene diamine tetramethylene phosphonate injection, sodium fluoride



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***Pharmacovigilance Programme of India for Assuring Drug Safety***

**ADVICE ABOUT REPORTING**

**A. What to report**

- Report serious adverse drug reactions. A reaction is serious when the patient outcome is:
  - Death
  - Life-threatening
  - Hospitalization (initial or prolonged)
  - Disability (significant, persistent or permanent)
  - Congenital anomaly
  - Required intervention to prevent permanent impairment or damage
- Report non-serious, known or unknown, frequent or rare adverse drug reactions due to Medicines, Vaccines and Herbal products.

**B. Who can report**

- All healthcare professionals (Clinicians, Dentists, Pharmacists and Nurses) can report adverse drug reactions

**C. Where to report**

- Duly filled Suspected Adverse Drug Reaction Reporting Form can be send to the nearest Adverse Drug Reaction Monitoring Centre (AMC) or directly to the National Coordination Centre (NCC).
- Call on Helpline (Toll Free) 1800 180 3024 to report ADRs.
- Or can directly mail this filled form to pvpi@ipcindia.net or pvpi.ipcindia@gmail.com
- A list of nationwide AMCs is available at:
  http://www.ipc.gov.in, http://www.ipc.gov.in/PvPI/pv_home.html

**D. What happens to the submitted information**

- Information provided in this form is handled in strict confidence. The causality assessment is carried out at AMCs by using WHO-UMC scale. The analyzed forms are forwarded to the NCC through ADR database. Finally the data is analyzed and forwarded to the Global Pharmacovigilance Database managed by WHO Uppsala Monitoring Centre in Sweden.
- The reports are periodically reviewed by the NCC-PvPI. The information generated on the basis of these reports helps in continuous assessment of the benefit-risk ratio of medicines.
- The information is submitted to the Steering committee of PvPI constituted by the Ministry of Health & Family Welfare. The Committee is entrusted with the responsibility to review the data and suggest any interventions that may be required.

**E. Mandatory field for suspected ADR reporting form**

- Patient initials, age at onset of reaction, reaction term(s), date of onset of reaction, suspected medication(s) and reporter information.

***For ADRs Reporting Call on PvPI Helpline (Toll Free)***

***1800 180 3024***

*(9:00 AM to 5:30 PM, Working Days)*

**Figure 2:** Back side of suspected adverse drug reaction reporting form

($^{18}$F) injection, sodium iodide ($^{131}$I) capsules for diagnostic use, sodium iodide ($^{131}$I) capsules for therapeutic use, sodium iodide ($^{131}$I) solution, sodium pertechnetate ($^{99m}$Tc) injection (Fission), sodium pertechnetate ($^{99m}$Tc) injection (Nonfission), sodium phosphate ($^{32}$P) injection, technetium ($^{99m}$Tc) DMSA injection, technetium ($^{99m}$Tc) DTPA Injection, technetium ($^{99m}$Tc) EC injection, technetium ($^{99m}$Tc) ECD injection, technetium ($^{99m}$Tc) glucoheptonate injection, technetium ($^{99m}$Tc) mebrofenin injection, technetium ($^{99m}$Tc) medronate complex injection, and technetium ($^{99m}$Tc) MIBI injection.[8]

The 10 RP monographs that were included in the Addendum-2015 are as follows: Gallium citrate ($^{67}$Ga) injection, strontium ($^{89}$Sr) chloride injection, technetium ($^{99m}$Tc) colloidal rhenium sulfide injection, technetium ($^{99m}$Tc) exametazime injection, technetium ($^{99m}$Tc) HYNIC-TOC injection, technetium ($^{99m}$Tc) macrosalb

injection, technetium ($^{99m}$Tc) mertiatide injection, technetium ($^{99m}$Tc) tetrofosmin complex injection, technetium ($^{99m}$Tc) trodat injection, and urea ($^{14}$C) capsules.[9]

## CLINICAL USE OF RADIOPHARMACEUTICALS

The RPs are the substances which are used for specific purpose either therapeutic or diagnostic, their dose and duration of action need to be monitored until the RPs present in the body of patients. During this period, the patient may suffer from some adverse reactions that can be reported to PvPI. So that, a data can be generated that could be useful for nuclear medicine physicians and experts for any regulatory intervention.

## ADVERSE DRUG REACTIONS INVOLVING RADIOPHARMACEUTICALS

Adverse reactions associated with the administration of RPs should be investigated and properly documented. Serious adverse reactions and problems with RPs should be reported to PvPI using any of the method described in the introduction section of this article.

The ADRs that pertains to RPs include faintness, pallor, diaphoresis, hypotension, anaphylactic reactions, dermographism, wheezing, bronchospasm, erythema, and pruritus. Drug interaction is also one of the major criteria that can be monitored or evaluated with the help of PV. The drug interactions that have been reported with RPs include nifedipine, digitalis, stilbestrol, gonadotrophins, phenothiazines, and cimetidine.[10] Policies and procedures should be developed that ensure that the correct patient receives the correct drug at the correct time, correct dose, and by correct route of administration.

ADRs have been defined by federal and state regulatory agencies and accreditation bodies (e.g., joint commission) and include a requirement for timely reporting. When reporting of such events is required, the report should be made to the appropriate agency within the time frame specified.

## CONCLUSION

Healthcare professionals are encouraged to report ADRs due to the use of RPs whether they have been used for diagnostic purpose or treatment.

PvPI is playing a leading role for the collection of data for a database on the Indian population due to ADRs of pharmaceuticals. The data related to RPs would help healthcare professionals who are dealing with RPs.

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### Conflicts of interest
There are no conflicts of interest.

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